

### **Amendments to Drawings**

Please delete Figure 6 from the drawings.

### REMARKS

The present invention relates to directing the differentiation of isolated mesenchymal stromal cells ("MSCs") into astrocytes for transplantation into a human patient with a central nervous system ("CNS") disease, disorder or condition.

Claims 1-18 are currently pending in the application. Claims 9-15 have been withdrawn from consideration as being drawn to non-elected inventions and claims 8 and 16 have been canceled. Therefore, claims 1-7 and 17-18 are currently under consideration. Claim 17 has been amended to remove a feature that is drawn to non-elected subject matter. Claim 1 has been amended to specify that the isolated stromal cell is directed to differentiate into an astrocyte and that the isolated stromal cells are pre-differentiated by coculturing in the presence of astrocytes. Support for this amendment can be found in the Examples, specifically in Examples 7 and 8. Thus, no new matter has been added by way of this amendment.

### Election/Restrictions

The Examiner states at page 2 of that Office Action that on the one hand, the election made on March 25, 2005 was made without traverse, and then on the other hand, that the present application contains claims 9-15 drawn to an invention nonelected with traverse in a reply filed 3/25/06 and that a complete reply to the final rejection must include a cancellation of nonelected claims or other appropriate action (See MPEP §821.01). Applicants would like to point out to the Examiner that the election made on 3/25/06 was made without traverse. Further, claims 9-15 were withdrawn in an amendment that was subsequently filed on October 24, 2005. Therefore, these claims are in compliance with MPEP §821.01 and Applicants respectfully requests a withdrawal of this objection.

### Claim Objections

The Examiner has objected to claim 17 because it comprises non-elected subject matter. Therefore, Applicant has amended claim 17 to delete the phrase "introducing isolated nucleic acid into said cells." By this amendment, claim 17 no longer encompasses withdrawn subject matter and Applicants respectfully request that the Examiner withdraw this objection.

### Objections to Drawings

The Examiner has objected to Figure 6. Specifically, the Examiner contends that Figure 6 does not clearly identify which sections pictured in Figure 6 correspond to day 4, 14, 30, or 72, as disclosed in the specification. While Applicants heartedly disagree with the Examiner's reading of Figure 6, in a good faith effort to expedite prosecution, Applicant has deleted Figure 6 as well as the corresponding descriptions and references from the specification. Applicants respectfully request that the Examiner reconsider and withdraw his objection in light of this amendment.

### Rejection of claims 1-8 and 16-18 pursuant to 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-8 and 16-18 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. Specifically, the Examiner reasserts his previous rejection in which he stated that Applicants would have had to conduct "undue experimentation" to make and/or use the claimed invention which encompasses *in vivo* differentiation of marrow stromal cells into cells of the central nervous system as a means of cell and/or gene therapy to treat a disease or disorder of the central nervous system. Applicants have canceled claims 8 and 16 which renders the rejection to these claims moot. Also, Applicants have amended claim 1 to recite a method of directing the differentiation of an isolated stromal cell into an astrocyte in a human patient suffering from a disease, disorder or condition of the CNS. The method comprises obtaining a bone marrow sample from a human donor, isolating stromal cells from the bone marrow sample, pre-differentiating the stromal cells by co-culturing them in the presence of astrocytes, and administering the isolated stromal cells to the CNS of the human patient by injection into the brain. In light of this amendment, Applicants respectfully submit that the claimed invention is enabled by the specification as filed under the current law pursuant to 35 U.S.C. § 112, first paragraph, for the following reasons.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably

omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Therefore, under the present patent law, claims 1-7 and 17-18, are enabled under 35 U.S.C. §112, first paragraph. More specifically, the disclosure provided by the specification as filed amply supports claims reciting a method of directing the differentiation of an isolated stromal cell into an astrocyte comprising the step of pre-differentiating the stromal cells by coculturing them in the presence of astrocytes. Applicants have demonstrated in Example 7 that human MSCs, when expanded and transplanted into a live animal, are able to migrate in a manner similar to astrocytes (page 52, lines 2-14). In fact, donor cells were found in multiple areas of the brain, including the contralateral cortex (page 52, lines 2-14) and the cells persisted in the sites to which they migrated. Further, Example 8 illustrates that when the human MSCs are co-cultured with astrocytes prior to transplantation, a percentage of the human MSCs stain positive for glial fibrillary acidic protein, which is an astrocytic marker. Taking these results together, Applicants have shown that human MSCs have the ability to differentiate into astrocytes and to migrate in a similar pattern as astrocytes when transplanted into the brain. These data demonstrate not only that MSCs behave in a similar manner to astrocytes when transplanted into the brain but also can be pre-differentiate into astrocytes when co-cultured with astrocytes prior to transplantation. Therefore, the disclosure provided by the specification as filed amply supports a claim reciting a method of directing the differentiation of an isolated stromal cell into an astrocyte.

The Examiner contends that the specification does not disclose the route of administration and the number of cells required for a therapeutic effect. Applicants point out that the claims have been amended to recite an injection method of administration. The specification demonstrates the successful reduction to practice of injection in that Example 7 discloses the injection of MSCs into the brain (page 47, line 8, to page 53, line 12). Thus, the skilled artisan, based upon the teachings of the invention, would have been able to practice the methods of the invention without undue experimentation. Accordingly, the skilled artisan would have understood that site of injection also depends on the site of injury and the disease being treated.

With respect to the number of cells to be administered, one skilled in the art would recognize, based upon the teachings of the specification as filed, that initial clinical trials could be performed by simple adjusting cell numbers used in the animal model disclosed by factoring in the weight and age of the patient as routinely performed in the art. Also, standard formulas for testing increasing dose levels are used in FDA prescribed Phase I or clinical trials and the skilled artisan routinely determined such dosages such that doing so would not be undue experimentation.

For the reasons discussed above, amended claim 1, and dependent claims therefrom, and claims 17-18, are amply enabled by the specification as filed. Therefore, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to claims 1-7 and 17-18 of the present application has been overcome or is now inapplicable, and that the claims are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of claims 1-8 and 17-18 is respectfully requested at the earliest possible date.

Respectfully submitted,

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June 16, 2006  
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Enclosure:   Petition for a three month extension of time and fee  
                  Copy of Notice of Acceptance of Power of Attorney  
                  Request for Continued Examination



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10/608,997	06/27/2003	Darwin J. Prockop	57616-5016CT1

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\*OC000000017681440\*


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## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

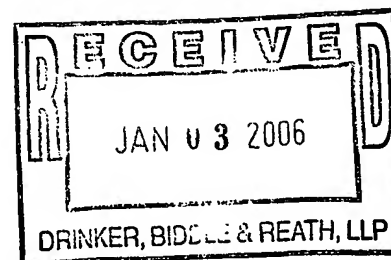
This is in response to the Power of Attorney filed 12/13/2005.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Docketed in CPI

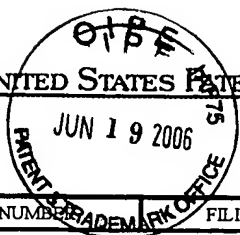
  
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### NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/13/2005.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).



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